A212 ROLE OF SYNDECAN-4 IN CHONDROCYTE DIFFERENTIATION

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Introduction Based on our previous data that the heparan sulfate proteoglycan syndecan-4 (Sdc4) is involved in cartilage breakdown during osteoarthritis, the authors analysed the distribution and functional role of syndecan-4 during endochondral ossification. The authors investigated this process during limb development in mouse embryogenesis and studied its contribution in fracture healing in adult bones, a process that in some respect recapitulates the sequence of biological events of endochondral ossification during skeletal development.

Methods The authors analysed syndecan-4 promoter activity in mouse embryos (E12- 17) by staining for β-galactosidase in *sdc4*$^{-/-}$ *lacZ* knock-in mice. For functional analysis, the authors assessed bone development in wild type and *sdc4*$^{-/-}$ animals by alcian blue/alizarin red staining and compared the expression of proteins implicated in cell proliferation and matrix remodelling (PCNA, ADAMTS-4, aggrecan neoepitopes) by immunohistochemistry. Fracture healing experiments were performed using 12-week-old female *sdc4*$^{-/-}$ and wild type mice and induced standardised, stabilised femur shaft fractures. Fractured and native femurs were dissected for biomechanical testing and maximum torque, angle at max. torque were determined, torsional stiffness was calculated. After 7, 14 and 28 days femurs were decalcified and embedded in paraffin. After alcian blue and Masson Goldner stainings, ratio of cartilage area and bone area to total callus area were measured.

Results At E12.0 a strong activity of the syndecan-4 promoter occurred at sites of cartilage condensations. In later stages syndecan-4 was detected in the growth plates of long bones. On the cellular level, syndecan-4 expression was detectable mainly in proliferative and hypertrophic chondrocytes. When the authors compared endochondral ossification in wt and *sdc4*$^{-/-}$ mice, they found the loss of syndecan-4 was associated with a marked inhibition of chondrocyte proliferation and a slight inhibition in the mineralisation of appendicular bones. This was accompanied by a loss of aggrecanase expression and a significantly reduced staining for ADAMTS generated aggrecan neoepitops in the epiphysial cartilage in E16.5 tibiae of *sdc-4* KO animals. In line with these data, histomorphometric analysis of fractured femurs from *sdc4*$^{-/-}$ mice demonstrated increased callus and cartilage formation compared to wild type mice in the early stage of fracture healing.

Conclusions Our data demonstrate that syndecan-4 is critically involved in chondrocyte differentiation during endochondral ossification. Loss of syndecan-4 affects proliferation and matrix remodelling by aggrecanases. These findings may be of relevance mainly during fracture healing in adult bones supporting existing evidence that syndecan-4 plays an important role in metabolic events under inflammatory conditions.